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Alterations in Resting-State Networks Following In Utero Selective Serotonin Reuptake Inhibitor Exposure in the Neonatal Brain

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ABSTRACT

BACKGROUND: Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression during pregnancy. SSRIs cross the placenta, inhibit serotonin reuptake, and thereby are thought to alter central fetal serotonin signaling. Both prenatal maternal mood disturbances and in utero SSRI exposure have been associated with altered fetal and infant behavior. Resting-state functional magnetic resonance imaging has identified resting-state networks (RSNs) in newborns, reflecting functional capacity of auditory and visual networks and providing opportunities to examine early experiences effects on neurodevelopment. We sought to examine the effect of in utero SSRI exposure on neonatal RSN functional organization. We hypothesized that prenatal SSRI exposure would be associated with alterations in neonatal RSNs compared with healthy control infants and infants exposed to mothers with depression.

METHODS: Clinician-rated Hamilton Depression Rating Scale and self-reported Pregnancy Experiences Scale were completed during the third trimester. Control (n = 17), maternal depression–exposed (Hamilton Depression Rating Scale ≥8 without SSRI exposure, n = 16), and SSRI-exposed (n = 20) 6-day-old neonates underwent resting-state functional magnetic resonance imaging. Independent component analysis was used as a data-driven approach to extract 22 RSNs.

RESULTS: SSRI-exposed neonates had higher connectivity in a putative auditory RSN compared with depressed-only (p = .01) and control (p = .02) infants (corrected for multiple comparisons), controlling for sex, age at the magnetic resonance imaging, and Pregnancy Experiences Scale score.

CONCLUSIONS: Hyperconnectivity in auditory RSN in neonates with in utero SSRI exposure relative to neonates of depressed but not pharmacologically treated mothers and control infants may offer an insight into the functional organization origins of shifts in language perception and altered language development, previously reported in infants and children with prenatal SSRI exposure.

Keywords: Maternal depression, Neonatal neurodevelopment, Resting-state functional MRI, Resting-state networks, Serotonin, SSRIs

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Mood disorders during pregnancy are common and carry risks for maternal health and infant social, behavioral, and cognitive development in infancy and childhood (1–9). Increasing use of selective serotonin reuptake inhibitor (SSRI) antidepressants used to treat perinatal mood disorders (10) adds risk for fetal and early neonatal development (11). SSRIs act primarily by the inhibition of the serotonin (5-hydroxytryptamine [5-HT]) transporter at the presynaptic neuron, increasing extracellular intrasynaptic serotonin levels (12). SSRIs freely cross the placenta (13) and have been shown to modulate fetal serotonin (5-HT) levels in animals (13) and in human infants' cord blood (14–16). 5-HT is widely distributed throughout the brain and is prevalent in regions involved in cognition, emotion regulation, and learning [reviewed in (11,17)]. Beyond its role as a neurotransmitter, 5-HT also plays a role as a trophic factor early in development, regulating aspects of neuronal differentiation, migration, myelination, and synaptogenesis (12). Therefore, early alterations of 5-HT signaling may have downstream consequences for serotonergic-related brain development and function.

In rodent models, early SSRI exposure during the period akin to the human third trimester was associated with increased depressive-like and anxiety-like behavior, together with a decrease in exploratory tendencies (18,19). Other animal studies have shown altered sensory (20) and auditory cortex functional properties (21). Early SSRI exposure was also associated with altered axonal development, raphe, and callosal connectivity in adult rats, with play behavior disruption and an exaggerated response to novel sounds in young rats (21).

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Long before birth, the impact of SSRI exposure is apparent. In human fetuses at 36 weeks' gestation, SSRI exposure was associated with reduced cerebral blood flow and reduced fetal heart rate variability (22). In addition, SSRI-exposed fetuses showed greater sensitivity to consonant voice onset time than nonexposed fetuses (23). In the newborn period, prenatal SSRI exposure has been associated with an increased rate of premature birth, decreased birth weight, increased risk for congenital malformations, and poor neonatal behavioral adaptation (24–26). Beyond the newborn period, early sensory and perceptual alterations have been reported (27,28), and neurodevelopmental and behavioral effects persist across the first years of life (24), possibly reflecting early altered brain development. Of particular note, shifts in language development during late fetal development and infancy that differentiate the impacts of SSRI exposure and maternal depression have been reported (23).

Reports examining the neural correlates of associations between prenatal SSRI exposure and neurodevelopment are emerging, suggesting that SSRI-exposed neonates have changes in white matter microstructure (29–31) and gray matter volume (31). While Jah *et al.* (29) showed fractional anisotropy decrease and mean diffusivity increase (indicative of maturation) in widespread tracts in SSRI-exposed neonates relative to control infants, Podrebarac *et al.* (30) showed opposite patterns in the superior white matter. It remains unclear whether these microstructural connections alterations are confounded by the severity of prenatal maternal depressive symptoms (29) or, in the case of very preterm infants antenatally exposed to SSRIs, by the degree of prematurity (30). In addition, Lugo-Candelas *et al.* (31) have shown increased amygdalar and insular gray matter volume together with increased amygdalar-insular white matter connectivity in prenatally SSRI-exposed infants compared with infants of depressed, nonpharmacologically treated mothers and control infants. Using electroencephalography, Videman *et al.* (32) showed prenatal SSRI exposure associations with reduced interhemispheric network connectivity, reduced frontal activation at slower frequencies, and reduced subcortical and cortical layers' coupling, suggesting both local and global effects of prenatal SSRIs on neonate brain activity.

In adults, distinct functional brain networks have been identified at rest (i.e., resting-state networks [RSNs]), including the default mode network [thought to support self-referential processes (33)] as well as visual-like and auditory-like RSNs. In early infancy, similar proto-RSNs are evident for some sensory systems (e.g., visual, auditory). This suggests that auditory and visual networks are functionally synchronized from birth, whereas networks associated with higher-order cognitive functions are established later (34–37), and therefore have different developmental trajectories (34,38,39).

Inherent to examining the potential effects of SSRI exposure is the effect of maternal mood disturbances on early brain development (40,41). Comparing infants of nonpharmacologically treated depressed mothers with infants of nondepressed mothers, Qiu *et al.* (42) showed that increased amygdala connectivity with the left temporal cortex, insula, anterior cingulate cortex, and ventromedial frontal cortex was positively correlated with increased maternal prenatal depressive symptoms (42). Such functional connectivity alterations of the amygdala are consistent with alterations observed in adult patients with major depressive disorder, reflecting possible developmental origins of neural circuits associated with an increased risk for depression. Functional connectivity alterations of the amygdala in infants of depressed mothers have also been reported by Posner *et al.* (43).

In the current study, we used newborns resting-state functional magnetic resonance imaging (fMRI) data to examine the effect of in utero exposure to SSRIs and maternal mood disturbances on functional connectivity organization and RSNs development in the neonatal brain. Given the previous findings associating functional alterations with prenatal SSRI exposure (29,31,32) and neonatal neurobehavioral disturbances associated with prenatal SSRI exposure (24), we hypothesized that in utero SSRI-exposed infants would have altered RSN functional organization compared with infants of depressed mothers not treated with SSRIs and control infants. However, as the current findings are sparse and this is the first study examining RSN organization in this population, we did not want to make any preliminary assumption and used a data-driven, unbiased approach to test our hypothesis.

METHODS AND MATERIALS

Participants

This study was approved by the University of British Columbia Clinical Research Ethics Board and the BC Women's Hospital Research Review Committee. Informed consent was obtained from mothers recruited during their second trimester of pregnancy, from a Reproductive Mental Health Clinic, midwifery services, and family physician clinics in metropolitan Vancouver, British Columbia, Canada. Healthy non–SSRI-treated, nondepressed pregnant women as well as nonpharmacologically treated depressed and SSRI-treated depressed pregnant women were recruited to the study (see additional information in the Supplement). All pregnant women treated with SSRIs had been diagnosed with a mood disorder and were prescribed an SSRI based on their clinical need.

Maternal Mood

Prenatal maternal mood was assessed at 26 and 36 weeks of gestation using the clinician-rated Hamilton Depression Rating Scale (HDRS) (44). Given that psychological experience related to pregnancy is not necessarily negative, in addition to the HDRS, we used a pregnancy-specific questionnaire for maternal appraisal of positive and negative experiences during pregnancy (Pregnancy Experiences Scale [PES]) (45) to assess another distinct dimension of maternal psychological experience related to pregnancy. HDRS depressive symptoms were used to form three maternal prenatal exposure groups: control infants with maternal HDRS <8, infants of a depressed mother with HDRS ≥ 8 with no drug exposure, and infants exposed to in utero SSRIs. The PES score targets pregnancy-related

maternal uplifts and hassles to specifically address how pregnant women experience their pregnancy, and was used as a covariate in our statistical model.

MRI Acquisition

A total of 96 pregnant women were recruited to the study. Of the 96 women, 12 women decided not to undergo the imaging component and hence did not contribute to the analyses reported below (see Supplemental Table S1). At postnatal day 6, 84 infants underwent MR scanning during natural sleep (n = 31 control infants, n = 24 depressed non–SSRI-exposed infants, n = 29 SSRI-exposed infants). Images were acquired on a pediatric-dedicated 3T MRI scanner (GE 750 Discovery; GE Healthcare, Milwaukee, WI) at the BC Children's Hospital MRI Research Facility in Vancouver, British Columbia, Canada. Infants were placed in an MR-compatible neonatal incubator (SREE Medical Systems [formerly Advanced Imaging Research], Cleveland, OH) that eliminated the need for sedation.

This study was part of larger scan series that included structural, microstructural, resting-state functional, and metabolic imaging. A 6-minute 20-second resting-state fMRI scan was acquired using echo-planar image sequencing (oblique axial, repetition time= 3000 ms; echo time = 18.4 ms, flip angle = 90°, 39 interleaved slices, 2 mm isotropic, no gap). For anatomical co-registration, T1 structural images were acquired using a three-dimensional fast spoiled gradient echo scan (echo time = 2.95 ms, repetition time = 7.7 ms), with a voxel size of $1 \times 1 \times 1$ mm^3 and reconstructed to 0.4 mm.

Image Preprocessing

Functional image analysis was carried out using FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Preprocessing was done using FEAT version 6.0 and included motion correction with MCFLIRT (46), nonbrain structure removal with BET (47), slice timing correction for interleaved acquisition, spatial smoothing using Gaussian kernel 3-mm full width at half maximum, grand-mean intensity normalization of the entire four-dimensional dataset, and high-pass temporal filtering (sigma = 50 seconds). Additional motion artifact correction was performed using FSL MELODIC (48) and AFNI 3dDespike (49). Registration to high-resolution structural or standard space [T1-weighted MR image of 40 weeks' gestation neonatal template (50)] images was carried out using FLIRT (46,51). In total, data from 53 infants were included in the analysis. Data from 21 infants were excluded owing to excessive motion (n = 3 sustained motion, n = 5 woke up during the scan), susceptibility (n = 6) and ghost (n = 1) artifacts, and technical error (n = 6). An additional 10 infants did not have resting-state functional data and were excluded from the study (n = 5 SSRI-exposed infants, n = 3 depressed only). Excluded infants were similar in all demographic measures to infants included in the final analysis ($p > .07$) (Supplemental Table S2). To evaluate motion parameters in our data, we measured two different parameters using MCFLIRT (46), in accordance with recent guidelines for analyzing neonatal resting-state fMRI (52): 1) absolute displacement (AD), which compares the transformation matrix at time point N with that of the reference time point, and 2) relative displacement (RD), which compares two subsequent time points, N and N + 1. For the majority of our subjects (n = 48), motion was minimal throughout the whole scanning session, with a maximal AD of <1 mm and a mean AD of 0.282 ± 0.20 mm, and an RD of 0.092 ± 0.05 mm. An additional 5 subjects (n = 3 SSRI exposed, n = 1 depressed only, n = 1 control infant) exhibited one or two episodes of motion in which the infants tilted their head away from the original position for 10 to 30 seconds and then titled their head back close to the original head position, and had higher levels of AD (ranged from 1 to 2.94 mm). For these five infants, following denoising with MCFLIRT (48) and AFNI 3dDespike (49), AD ranged between 0.02 and 0.06 mm. Overall, for all of our 53 subjects, AD ranged between 0.05 and 2.94 mm (mean 0.433 ± 0.55 mm) and RD ranged from 0.03 to 0.69 (mean = 0.11 ± 0.1). No significant group differences were detected ($p > .1$, using one-way analysis of variance). Following denoising, values for AD were reduced and ranged between 0.001 and 0.15 mm (mean = 0.032 ± 0.025 mm), and RD ranged from 0.001 to 0.04 (mean 0.019 ± 0.01 mm), with no group differences ($p > .7$ using one-way analysis of variance).

Statistical Analyses

Model-free probabilistic independent component analysis (ICA)–based exploratory data analysis was carried out using MELODIC version 3.14 (48), applied to each individual infant's blood oxygen level–dependent preprocessed time series. ICA was used to investigate the possible presence of unexpected artifacts or spatiotemporal resting-state patterns of activation (see Supplement). To assess the consistency of independent components across all infants at the group level, ICA analysis was then carried out using a temporal concatenation approach with MELODIC (48). This yielded group independent component maps that were thresholded at $p < .05$ to control for the false discovery rate for each RSN map (48). First, we created an averaged RSN template from 30 infants (10 randomly selected infants from each of the three groups, using a random number generator), which unbiasedly represents all the groups in our sample to serve as a reference for group comparison, which was carried out using dual regression. In short, the spatial maps from the group-average analysis were used to produce subject-specific versions of the group's spatial maps, and associated time series, using dual regression (53), resulting in a set of subject-specific spatial maps, one per group-level spatial map.

We then tested between-group differences to compare between control, depressed-only, and SSRI-exposed infants. As a first step we ran the analysis with no control variables. Next, to reduce the need for additional correction for multiple networks, based on the results from the first analysis, the second analysis was focused only on networks showing differences between groups (42). To calculate between-group differences, we used FSL's randomize permutation-testing tool with a general linear model (53) adjusted for postmenstrual age at the MRI scan and sex. In addition, we included mean PES scores (45), focusing on measures that differed between groups (Table 1).

Table 1. Demographics

	Entire Sample (N = 53)	Control Group (n = 17)	Depressed-Only Group (n = 16)	SSRI-Exposed Group (n = 20)	p Value
Maternal Characteristics					
Age, years[a]	34.62 ± 3.75	32.92 ± 2.79	33.79 ± 2.02	36.75 ± 4.55	.003
SSRI duration, days	–	–	–	258.9 ± 33.8	–
SSRI dose at 36 weeks' gestation, mg	–	–	–	41.31 ± 50.84	–
Education, years	17.79 ± 3.02	18.71 ± 3.01	17.56 ± 3.34	17.2 ± 2.7	.305
Smoking per pregnancy (number of cigarettes)	0.02 ± 0.14	0.00 ± 0.00	0.00 ± 0.00	0.05 ± 0.24	.447
Alcohol per pregnancy (number of single drinks)	0.83 ± 3.16	0.59 ± 2.45	0.44 ± 1.31	1.35 ± 4.53	.65
Prenatal HDRS (third-trimester average)[a]	9.00 ± 4.39	4.911 ± 1.82	10.687 ± 3.17	11.12 ± 4.47	<.001
Prenatal PES HASS frequency (third-trimester average)	7.69 ± 1.96	6.76 ± 2.27	8.21 ± 1.85	7.8 ± 1.76	.098
Prenatal PES uplift frequency (third-trimester average)	9.07 ± 1.21	9.29 ± 0.86	9.5 ± 0.68	8.8 ± 1.18	.085
Prenatal PES uplift intensity (third-trimester average)	2.15 ± 0.40	2.16 ± 0.47	2.15 ± 0.35	2.14 ± 0.39	.982
Prenatal PES HASS intensity (third-trimester average)[a]	1.62 ± 0.39	1.37 ± 0.33	1.61 ± 0.32	1.84 ± 0.38	.001
Neonatal Characteristics					
Type of delivery (vaginal/C-section)	36/17	14/3	12/4	10/10	.087
Gestational age at birth, weeks	39.53 ± 1.67	39.9 ± 1.81	39.84 ± 1.60	38.97 ± 1.53	.165
Age at the MRI, hours	251.43 ± 193.95	199.85 ± 161.01	292.58 ± 217.94	262.53 ± 199.23	.378
Sex, male/female	30/23	12/5	10/6	8/12	.154
Birth weight, kg	3.43 ± 0.49	3.48 ± 0.36	3.55 ± 0.45	3.29 ± 0.59	.272
Birth length, cm[a]	51.1 ± 2.37	51.89 ± 1.46	52.09 ± 2.28	49.62 ± 2.41	.001
Head circumference, cm	34.66 ± 1.55	34.78 ± 1.77	34.79 ± 1.62	34.42 ± 1.44	.706
1-minute Apgar score[a]	7.58 ± 2.10	8.18 ± 1.5	8.19 ± 1.94	6.6 ± 2.37	.027
5-minute Apgar score	8.66 ± 1.02	9.00 ± 0.0	8.81 ± 0.91	8.25 ± 1.37	.061
NAPI irritability score[b]	66.938 ± 18.32	68.28 ± 17.8	69.96 ± 18.27	62.3638 ± 17.81	.548

Values are mean ± SD or n/n.

HASS, hassles; HDRS, Hamilton Depression Rating Scale; MRI, magnetic resonance imaging; NAPI, Neurobehavioral Assessment of the Preterm Infant; PES, Pregnancy Experiences Scale; SSRI, selective serotonin reuptake inhibitor.

[a]Significant difference using one-way analysis of variance.

[b]Data were available for 41 infants (n = 15 control group, n = 13 depressed-only group, n = 13 SSRI-exposed group).

RESULTS

Participant Characteristics

Table 1 presents both the maternal and neonatal characteristics for the whole group (N = 53) and for the control (n = 17), depressed-only (n = 16), and SSRI-exposed (n = 20) groups. Independent-sample t tests revealed no group differences in maternal education, alcohol use, or smoking ($p > .085$). SSRI-treated mothers and depressed, nonpharmacologically treated mothers had significantly higher HDRS scores and higher PES hassle intensity scores compared with control mothers. No group differences were found in birth weight, gestational age, or head circumference ($p > .05$). However, SSRI-exposed infants had lower birth length and Apgar scores at 1 minute compared with the other groups. In addition, measures of irritability using Neurobehavioral Assessment of the Preterm Infant (54) did not differ between groups (p = .548).

Between-Group Differences (Control vs. Depressed vs. SSRI-Exposed Infants)

We used a dual-regression general linear model (53) (Table 2) to compare between the control, depressed-only, and SSRI-exposed groups. First we ran the analysis using no confounder variables. Significant group differences were evident in an RSN similar to the putative auditory network (Figure 1; see also Supplement for the RSN template from 30 randomly selected infants). Figure 2A (see also top two rows of Table 2) shows clusters where significant hyperconnectivity was observed for a main effect in the SSRI-exposure group for the auditory network compared with the control group, and compared with infants of depressed mothers not treated with SSRIs (Figure 2B), while other group comparisons (i.e., control group vs. depressed-only group) were not significantly different ($p > .1$). Overall, the SSRI-exposed group showed hyperconnectivity within the auditory network, and in regions that were coactivated with the network.

Building on the results of the first analysis, we then ran a second analysis to examine the specific effects of SSRI exposure on the putative auditory network, accounting for sex, age at the MRI scan, and maternal PES score. Results revealed significant hyperconnectivity in the SSRI-exposed group compared with the control (p = .02) (Figure 3A) and depressed-only (p = .01) groups (see Figure 3B), corrected for multiple comparisons in the auditory network (Figure 1). Figure 3B (see also bottom rows of Table 2) shows the clusters where significant blood oxygen level–dependent signal differences were observed, stemming from a larger

Table 2. Summary of Dual-Regression GLM Analysis

Statistical Model	Size (Voxels)	Peak of Activation (Voxel) X	Y	Z	Color	Estimated Regions	*p* Value	Effect Size
Dual-Regression GLM Without Covariates (Figure 2A)								
SSRI-exposed group vs. control group	661	5	15	20	Blue	Supramarginal gyrus (L)	.010	0.327
						Frontal inferior orbital gyrus (R)	.024	0.322
						Temporal inferior gyrus (R)	.033	0.319
						Temporal medial gyrus (R)	.038	0.317
						Frontal inferior triangularis gyrus (R)	.029	0.320
						Angular gyrus (L)	.038	0.317
	21	6	7	11	Red	Occipital inferior gyrus (L)	.034	0.319
						Temporal inferior gyrus (L)	.048	0.314
SSRI-exposed group vs. depressed-only group	417	6	21	10	Green	Temporal pole superior (L)	.011	0.332
						Insula (L)	.011	0.332
						Frontal inferior operculum gyrus (L)	.022	0.328
						Putamen (L and R)	.013	0.331
						Temporal superior gyrus (L)	.045	0.320
						Heschl gyrus (L)	.048	0.319
	36	20	14	9	Purple	Temporal inferior gyrus (R)	.035	0.324
						Temporal medial gyrus (R)	.046	0.320
Dual-Regression GLM With Covariates (Figure 2B)								
SSRI-exposed group vs. control group	552	13	15	21	Gray	Paracentral lobe (R)	.022	0.323
						Parietal inferior lobe (R and L)	.045	0.315
						Occipital inferior cortex (L)	.043	0.316
						Temporal superior gyrus (L and R)	.041	0.316
						Heschl gyrus (R)	.045	0.315
						Angular gyrus (L)	.041	0.316
	25	20	21	17	Green	Precentral gyrus (R)	.038	0.317
						Frontal medial gyrus (R)	.048	0.314
	21	13	26	19	Orange	Frontal superior medial gyrus (R)	.042	0.316
						Frontal superior gyrus (R)	.042	0.316
	16	10	13	12	Red	Lingular gyrus (L)	.045	0.315
	13	15	20	12	Blue	Globus pallidus (R)	.049	0.314
	10	12	8	17	Yellow	Cuneus (R)	.040	0.317
SSRI-exposed group vs. depressed-only group	418	16	22	12	Dark green	Putamen (R)	.010	0.332
						Globus pallidus (R)	.019	0.329
						Frontal inferior operculum gyrus (L)	.026	0.327
						Rolandic operculum (L)	.026	0.327
						Thalamus (L)	.036	0.323
						Temporal superior gyrus (L)	.022	0.328
	40	17	8	13	Yellow	Occipital inferior cortex (L)	.038	0.320
						Occipital medial gyrus (R)	.042	0.321
	16	20	18	15	Blue	Rolandic operculum (R)	.044	0.321
	13	17	11	12	Red	Fusiform gyrus (R)	.036	0.323
						Lingular gyrus (R)	.043	0.321
	11	21	15	11	Light green	Temporal medial gyrus (R)	.048	0.319
						Temporal superior gyrus (R)	.044	0.321
	11	19	11	11	Purple	Temporal inferior gyrus (R)	.044	0.321

The size of the cluster is given using a threshold of 0.05. All the clusters were found for the auditory resting-state network (Figure 1). Edinburgh Neonatal Atlas (ENA33) (68) was used to identify the brain regions. The *p* values were corrected for multiple comparisons. Conservatively, effect sizes are computed using Cohen's *d* (calculator 5 from https://www.psychometrica.de/effect_size.html) assuming independency. Effect sizes would have been higher if we would have assumed dependency.

GLM, general linear model; L, left; R, right; SSRI, selective serotonin reuptake inhibitor.

blood oxygen level–dependent signal in regions in the temporal, frontal, angular, and occipital cortices. We also analyzed the data using gestational age at birth instead of age at the MRI, and found similar results (SSRI group vs. control group: $p = .018$; SSRI group vs. depressed-only group: $p = .012$). However, as infants in our cohort were born full-term,

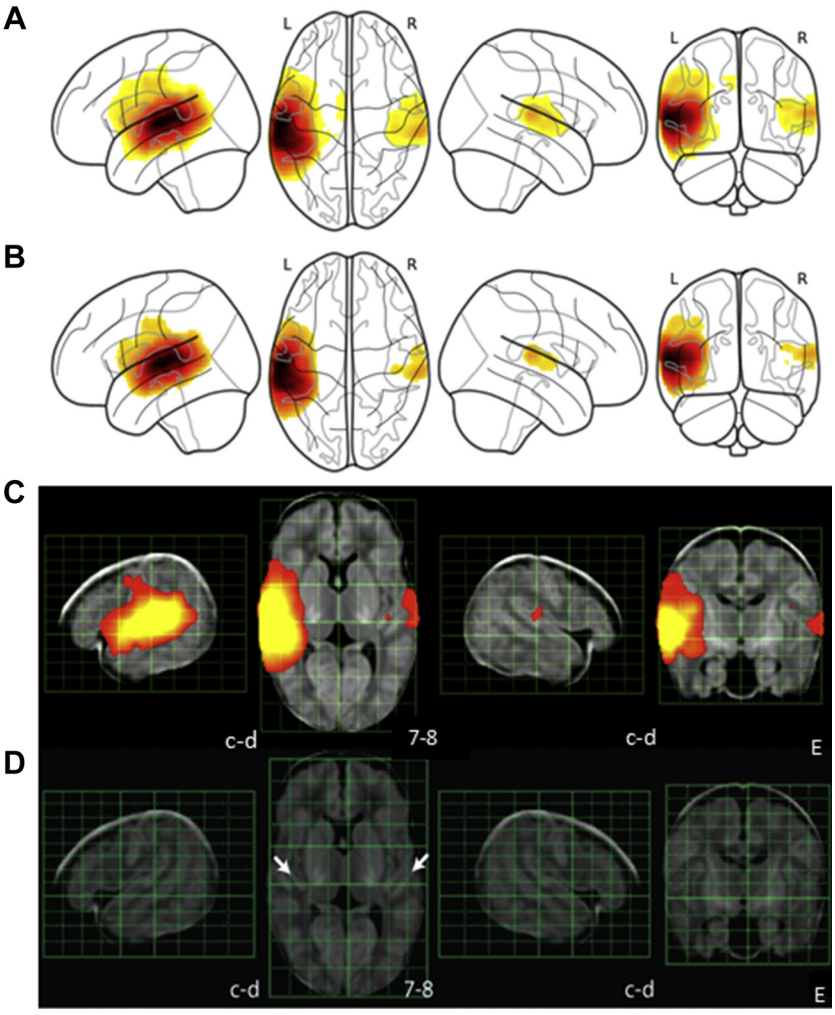

Figure 1. Independent component analysis (ICA) component in the putative auditory network in neonatal template space (50) realigned to the anterior commissure-posterior commissure line plane. **(A)** Glass brain showing the ICA network thresholded at 2.9 (typical threshold for ICA networks). **(B)** The same ICA network more stringently thresholded at 4. **(C)** The same network shown on the neonatal template image thresholded at 4. The grids represent Talairach slices, as outlined in Talairach and Tournoux (67), and highlight the primary auditory cortex. Note that the correlated ICA activations are centered in the superior temporal gyrus. **(D)** Anatomical underlay for the ICA activations. Note that the activations are centered on Heschl's gyrus bilaterally (arrows). This anatomical localization of data-driven ICA components in the primary auditory cortex strongly suggests that this network represents an auditory network. L, left; R, right.

we used age at the MRI in the analysis as a more critical reflection of brain functional growth, inherent to post-conceptual age.

DISCUSSION

In this study, we found an association between prenatal SSRI exposure and increased functional connectivity synchronization or hyperconnectivity of RSNs in the newborn infant, relative to control infants and infants of nonpharmacologically treated depressed mothers. Using a data-driven approach, we studied overall MR-derived resting-state functional effects without limiting ourselves to specific brain regions or networks. Newborns exposed to SSRIs in utero exhibited differences in the pattern of activation of a component, which is qualitatively similar to an auditory network previously shown in similar populations using ICA analysis of resting-state fMRI data (38,39) and an auditory task-based fMRI approach (55). These differences remained even when we adjusted for mother's pregnancy-related negative experiences and for sex and infants' age at the scan. These differences stemmed from hyperconnectivity in regions within the auditory network in the temporal cortex and parietal lobe. Group differences were also seen in nonauditory regions, with positive, albeit weak, associations with the auditory network in frontal and visual regions. Interestingly, in a recent neuroimaging study of functional connectivity in preterm infants, Thomason *et al.* (56) demonstrated that fetuses who were eventually born preterm had lower levels of functional connectivity synchronization in regions associated with the auditory network, which is considered a prelingual network hypothesized to develop into language processing regions with maturation. In contrast, our results showed hyperactivation of regions functionally associated with the auditory network in SSRI-exposed infants, suggesting a special sensitivity of these regions to different in utero experiences. Consistent with this interpretation, Gao *et al.* (34) demonstrated that the auditory network is one of the earliest networks to develop: functional connections within the network are already synchronized at birth and resemble "adult-like" patterns of activation. Moreover, studies exploring developmental trajectories of the auditory network and other early networks showed that the auditory network, compared

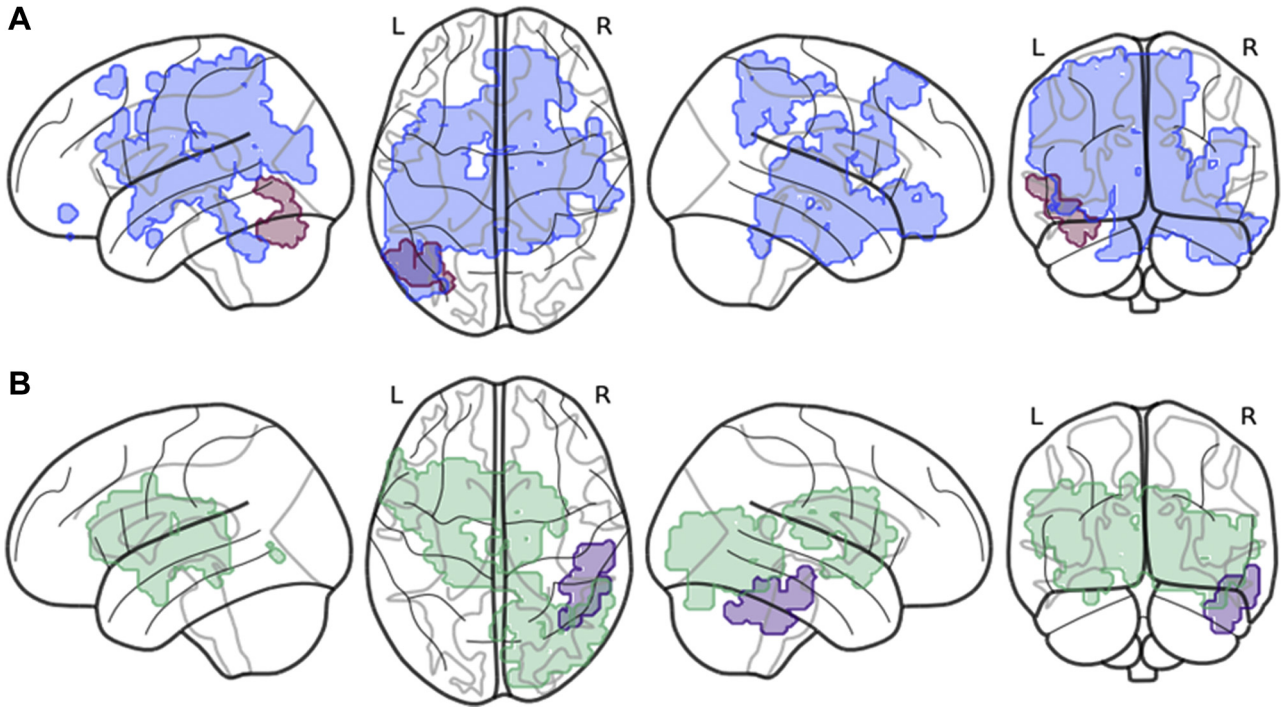

Figure 2. Selective serotonin reuptake inhibitor (SSRI)–exposed infants (n = 20) show greater blood oxygen level–dependent signal compared with depressed-only (n = 16) and control (n = 17) infants. Dual regression results registered to a neonatal template space (50) of the three group comparison (SSRI-exposed vs. depressed-only vs. control infants) using a general linear model relative to the resting-state network template (Figure 1). The Edinburgh Neonatal Atlas (ENA33) (68) was used to identify the brain regions. Colored clusters in sagittal, axial, and coronal views show significant hyperconnectivity in regions coactivated with the auditory network (corrected for multiple comparisons). **(A)** Dual-regression results of independent components representing the auditory network with no covariates comparing SSRI-exposed infants with control infants (voxel dimension = 4 mm isotropic). Differences are shown in regions that are both within the auditory network, such as the left angular cortex, and also in nonauditory regions, such as the left occipital inferior gyrus with positive, albeit weak, associations with the auditory network that were larger for the SSRI-exposed group compared with the control group (p = .01). **(B)** Dual regression results of the independent components representing the auditory network with no covariates comparing SSRI-exposed infants with infants of non-pharmacologically treated depressed mothers (voxel dimension = 4 mm isotropic). Differences are shown in regions that are both within the auditory network, such as the left Heschl's gyrus, and also in nonauditory regions, such as the left insula, with positive, albeit weak, associations with the auditory network that were larger for the SSRI-exposed group compared with the depressed-only group (p = .013) (see also Table 2). L, left; R, right.

with other networks, such as the dorsal attention and default mode networks, exhibits only minimal maturational changes in the first year of life (34,38,39), reflected by reduced connectivity strength (specialization) thought to be related to pruning processes (34). Therefore, it is reasonable to speculate that the auditory network might be more susceptible to the intrauterine environment, as a significant amount of its maturation occurs during prenatal development. Indeed, negative experiences during pregnancy, as assessed by the PES of intensity of hassles, are positively correlated with neurological maturation, as reflected in shorter brainstem auditory evoked potential latencies (57).

Our findings are consistent with functional organization alterations reported in animal studies (21,58). In rodents, early 5-HT manipulations have been associated with altered raphe and callosal connections, sensory processing, and myelin sheath formation (21,59). However, it is not clear whether these central 5-HT signaling changes, which reflect constrained downstream neural development, are also present in humans.

Although the functional consequences of increased functional connectivity synchronization in the auditory networks is yet to be fully understood, a previous study in our lab on a different cohort reported on shifts in language perception in SSRI-exposed infants possibly reflecting accelerated language development compared with both healthy control infants and infants of symptomatic non–SSRI-treated depressed mothers during the first year of life (23). This study indicated that even before birth, SSRI-related accelerated development of language (speech sound) perception is already evident. Weikum *et al.* (23) reported that at 36 weeks' gestation, fetuses exposed to SSRIs could discriminate not only similar-sounding vowels [as has previously been reported in utero (59)], but also similar-sounding consonants (e.g., *ta* vs. *da*). Control fetuses not exposed to SSRIs were able to discriminate only between similar-sounding vowels, but not between similar-sounding consonants, as expected for this developmental stage. These findings were taken as evidence of an SSRI-related acceleration in auditory-perceptual development (23). Differences between the SSRI-exposed infants and the nonexposed infants were also apparent following birth. Young infants show perceptual sensitivities that enable them to discriminate speech-sound differences in both their native and in unfamiliar languages, but as they establish the speech sound categories used in their native language, they stop discriminating

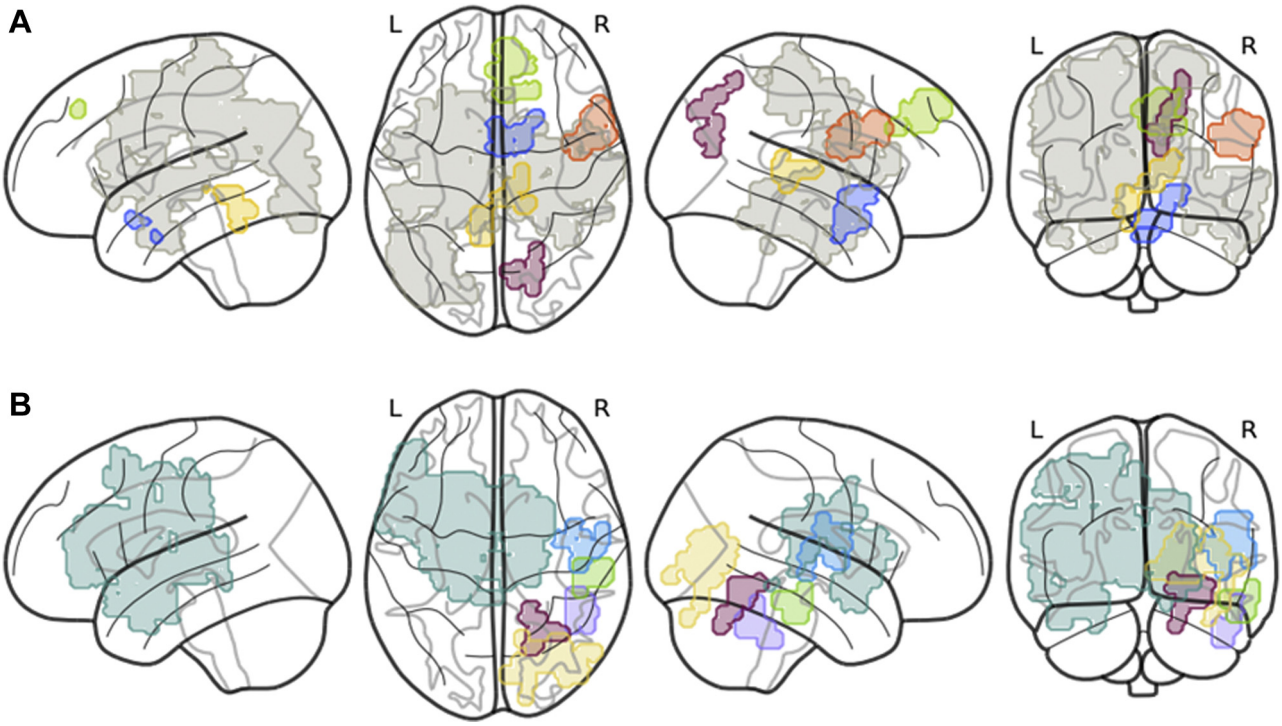

Figure 3. Dual regression for the independent component analysis component representing the auditory network, including the following covariates: postmenstrual age at magnetic resonance imaging, sex of the infant, and average maternal Pregnancy Experiences Scale score for intensity of hassles in the third trimester of pregnancy. **(A)** Dual-regression results for the independent component analysis component representing the auditory network comparing selective serotonin reuptake inhibitor (SSRI)–exposed infants with control infants (voxel dimension = 4 mm isotropic). Differences are shown in regions that are both within the auditory network, such as the superior temporal cortex and the left angular gyrus, and also in regions outside of the auditory network, such as the left occipital inferior gyrus, with positive, albeit weak, associations with the auditory network that were larger for the SSRI-exposed group compared with the control group (p = .022). **(B)** Dual-regression results for the independent component analysis component representing the auditory network comparing SSRI-exposed infants with infants of nonpharmacologically treated depressed mothers (voxel dimension = 4 mm isotropic). Differences are shown in regions that are both within the auditory network, such as the superior temporal cortex, and also in regions outside of the auditory network, such as the right fusiform gyrus, with positive, albeit weak, associations with the auditory network that were larger for the SSRI-exposed group compared with the depressed-only group (p = .01) (see also Table 2). L, left; R, right.

nonnative speech sound differences. In the Weikum *et al.* (23) study, the control infants showed this pattern. However, the SSRI-exposed infants performed at 6 months like typically developing infants do at 10 months, and were already discriminating between nonnative speech-sound differences, while infants of nonpharmacologically treated depressed mothers responded to nonnative language only at 10 months (23). Such developmental shifts in language development may reflect an acceleration in the closure of a critical period "window" for early language discrimination associated with prenatal SSRI exposure (23). Although we cannot infer a causal relationship, it might be that hyperconnectivity within the auditory network in newborn infants could help explain the accelerated speech perception development seen in prenatally SSRI-exposed fetuses and infants.

While it may seem that accelerated language perception in the first year of life (23) or hyperconnectivity in the auditory network could result in neurodevelopmental benefits for the infant that might be advantageous for subsequent language development, in fact it is more often the case that asynchrony in developing systems is detrimental to long-term development. If the auditory network has developed before the infant accrues sufficient exposure to his or her native language and before the development of the cognitive skills to begin learning language, then later deficits could emerge. And indeed, a number of studies have suggested long-term negative associations between prenatal SSRI exposure and expressive language development (60), and possible associations between prenatal SSRI exposure and poorer capabilities of verbal fluency (61). Others have reported on increased risk of speech and language disorders, such as expressive language disorder and receptive language disorder (62), and risk for autism spectrum disorder (63). Importantly, the long-term effects of the prenatal environment, and the postnatal environment, also play a role in shaping neurodevelopment (64). The in utero environment "prepares" the fetus for life outside the womb (65). According to the predictive adaptive hypothesis, in cases in which these expectations are not met, it is, at least to some extent, the capacity of an individual to cope with these mismatches between the in utero environment and the postnatal environment that may put an infant at risk for future psychopathology (66). Longitudinal studies examining both pre- and postnatal environmental aspects, using both functional connectivity imaging and evaluation of language perception and proficiency development, might be able to better address these questions.

Surprisingly, infants of nonpharmacologically treated depressed mothers did not show a significant alteration compared with control infants. It might be that, although there were substantial clinical differences in mood symptom severity in our cohort, mild symptoms were observed (HDRS: 10.68 ± 3.1 for depressed-only group, 4.91 ± 1.82 control group, 11.31 ± 4.49 for SSRI-treated group) (see Table 1). Thus, such symptoms might not have been sufficiently severe to alter the functional connectivity patterns in the auditory network. Subsequent studies are warranted to test whether increased mood symptoms might be associated with alterations of the functional organization of RSNs.

Mothers treated with an SSRI might be inherently different from depressed mothers not treated with an SSRI for a mood disturbance during pregnancy. While we included both SSRI-treated and non–SSRI-treated-depressed women and adjusted for pregnancy-related experiences, the effect of residual confounding related to maternal mood disturbances, such as illness severity, and genetic factors inherent to mood disorders (i.e., confounding by indication) could not be completely ruled out. Owing to the challenges inherent to studying mothers and their neonates in this setting (i.e., maternal dropout owing to unpredictable nature of perinatal depression, or success rate per scan), our final sample size was ultimately reduced. Future studies are needed to replicate these findings with larger cohorts and a wider range of depressive and stress symptoms to allow us to account for as-yet-unmeasured potential confounders.

Additional limitation of our study is that our sample size did not allow us to further investigate dose-related effects or to subdivide the SSRI-exposed group to the different types of SSRIs. Larger cohorts of infants should address the questions of whether different type or dosage of SSRI have an effect on the infant's resting-state network patterns of activation.

In summary, in this study we used a nonbiased approach to examine possible associations between in utero exposure to SSRIs and development of functional organization of RSNs in neonates. We found that SSRI exposure was associated with hyperconnectivity in the coactivation of the auditory network compared with control infants and with infants of nonpharmacologically treated depressed mothers. In light of previous findings showing accelerated auditory capacity of language perception's effect of in utero exposure to SSRIs, our results might serve to advance our understanding of a possible developmental acceleration associated with prenatal SSRI exposure. Further, to control for different aspects of the maternal prenatal in utero environment, we used an analytic model that included a nonpharmacologically treated depressed group, and also accounted for the intensity of pregnancy-related negative experiences, which differed between groups. Our study is the first to show an association of in utero SSRI exposure on functional connectivity patterns in the auditory network of the newborn infant. The implication of these positive associations is yet to be determined.

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